

Intravenous pamidronate treatment of polyostotic fibrous dysplasia associated with the McCune Albright syndrome

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Objectives: An open trial of pamidronate treatment was undertaken in 5 children and 4 young adults with polyostotic fibrous dysplasia associated with McCune Albright syndrome to assess clinical response, bone turnover, and cardiovascular status over a 2-year period.

Study design: Pamidronate was administered by intravenous infusion 1 mg/kg/d for 3 days every 6 months for 2 years. Bone turnover was measured at 0, 6, 12, 18, and 24 months with bone mineral density, and cardiac output was assessed by echocardiography at 0, 12, and 24 months.

Results: All subjects reported marked reduction in bone pain and sustained increased mobility. The fracture rate decreased in most. Orthopedic insertion of intramedullary rods was successful with maintenance of rod position. Mean osteocalcin levels fell from $35.5 \pm 5.6 \mu\text{g/L}$ to $28.4 \pm 4.1 \mu\text{g/L}$ ($P < .03$). Other bone turnover marker changes were not significant. The mean bone mineral density at lumbar spine increased from 0.5 ± 0.08 to $0.67 \pm 0.03 \text{ g/cm}^2$ ($P < .002$) in children and 1.16 ± 0.6 to $1.33 \pm 0.08 \text{ g/cm}^2$ in adults ($P < .005$). Other changes in bone mineral density were not significant. Cardiac output did not change significantly.

Conclusions: Pamidronate treatment is an effective therapeutic modality for children with polyostotic fibrous dysplasia, with a good short-term safety profile. Failure to demonstrate major biochemical or bone densitometry improvements is due to the nature of the fibrous dysplasia and intercurrent microfracture. (J Pediatr 2000;137:403-9)

markedly limits activities are all major problems in affected children.

See related article, p. 410.

Bisphosphonates are stable analogs of naturally occurring pyrophosphate that are clinically effective in disorders associated with increased bone resorption such as Paget's disease, bone metastases, and osteoporosis. Chemical modifications in the side chain chemistry can greatly increase their potency. The molecular basis of bisphosphonate action is complex, with a cumulative inhibitory effect on pathologic bone loss. Bisphosphonates inhibit bone resorption by being adsorbed and taken up onto mineral surfaces in bone, where they interfere with osteoclast action.⁵⁻⁸ Bisphosphonates may also act by stimulating osteoblasts to produce an osteoclast inhibitory factor.

BMD Bone mineral density
PFD Polyostotic fibrous dysplasia

The McCune Albright syndrome is characterized by polyostotic fibrous dysplasia, café au lait pigmentary changes, and autonomous hyperfunction of endocrine glands.^{1,2} PFD pro-

duces a multitude of bony disfigurements, recurrent fractures, and increasing deformity throughout childhood and adolescence. Ill health, recurrent hospitalization,^{3,4} and deformity that

Recent data suggest that impaired capacity for osteogenic differentiation found in mutated fibrous dysplasia cells may be mediated by changes in transforming growth factor β /BMP signaling systems.⁹ The use of bisphosphonates for treatment of patients with PFD was originally proposed on the basis that the large and numerous osteoclasts present at the interface between normal bone, and fibrous dysplasia could be responsible for increased osteoclast resorption, with histologic and biochemical similarities between fibrous dysplasia and Paget's disease.^{10,11} After the first de-

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Table I. Manifestations of clinical problems in subjects before commencement of treatment

Subject			Clinical signs other than fibrous dysplasia	Pubertal status	Other pathologic conditions	Annualized rate fracture in preceding 2 years
No.	Age (y)	Sex				
1	11	M	Tachycardia, cafe au lait markings	Testes 6 mL from age 7 (Prader)		5
2	5	M	Warm skin, tachycardia, cafe au lait markings	Testes 6 mL from age 5	Fatty degeneration on liver biopsy	2
3	9	M	Tachycardia, warm skin, cafe au lait markings	Prepubertal testes 3 mL		3
4	3	M	Tachycardia, warm skin, cafe au lait markings	Prepubertal testes 2 mL		4
5	6	M	Cafe au lait markings	Prepubertal testes 3 mL		2
6	17	M	Cafe au lait markings	History of puberty at age 13	L Inferior quadrantanopia, MRI normal	2
7	26	F		Menarche at age 10		0
8	25	F	Cafe au lait spots	History of menarche age 9		0
9	28	F	Cafe au lait spots	History of menarche age 12-13		1

MRI, Magnetic resonance imaging.

scription of bisphosphonate treatment for PFD was published in 1994, only a few studies of long-term effects of intravenous pamidronate use in PFD were published; there is only 1 study of the effect of treatment on children.^{10,12,13-16}

PATIENTS AND METHODS

This study involved 5 male children aged 3 to 11 years and 4 young adults (3 female, 1 male). Eight patients had the McCune Albright syndrome as defined by PFD and multiple large cafe au lait lesions, and 1 young adult had PFD without other manifestations of the McCune Albright syndrome (Table I). Four patients (1, 3, 4, and 5) were confined to wheelchairs or walked with crutches at all times before treatment. All others had major leg length discrepancies and walked with a severe limp. All patients reported chronic bone pain that caused sleep

disturbance and exacerbated clinical disability. Patients 1 to 5 had had numerous previous failed surgical procedures for fracture management with 7 past surgical insertions of rods, cross bolts, and plates, all of which became loose and were unsuccessful.

Patient 2 had abnormal liver function tests. Liver biopsy before the commencement of the study demonstrated fatty degeneration and infiltration only. Patients 1, 2, 3, and 4 had a chronic tachycardia and warm skin, suggestive of a high cardiac output state from the time of commencement of the study. All patients were euthyroid throughout the study.

No patient had any other endocrinopathy before or during the 2 years of treatment, although 2 of the young adult female patients reported having had menarche at age 9 to 10 years.

Patient 6 had a left inferior quadrantic field defect before the treatment was begun. Skull x-ray evaluation and magnetic resonance imaging failed to reveal any pituitary abnormality or

mass encroaching on the optic nerves or optic foramina.

A 2-year study was undertaken with documentation as to the effect of disodium pamidronate on the fibrous dysplasia and monitoring for any side effects of treatment. The project had the approval of the Ethics Committee of the Royal Children's Hospital. Informed consent was obtained from all participants and parents for the study.

All patients were admitted to the hospital for administration of disodium pamidronate by intravenous infusion. A dosage of 1 mg/kg was given over a 4-hour period each day for 3 consecutive days. Infusions were repeated every 6 months for 2 years. All patients had visual field testing (Goldman fields) performed at 0, 12, and 24 months. Thyroid function was monitored by free thyroxine levels and thyroid-stimulating hormone and pubertal status by follicle-stimulating hormone, luteinizing hormone, and testosterone levels at 0, 6, 12, 18, and 24 months.

Table II. Biochemical markers of bone turnover in children during treatment

	Time (mo)			Normal range	P value
	0	12	24		
Osteocalcin ($\mu\text{g/L}$)	35.5 ± 5.6	32.8 ± 3.8	28.4 ± 4.1	26-56	.03
Alkaline phosphatase (u/L)	818.5 ± 181.7	775.2 ± 197.5	654.0 ± 171	100-350	NS
Pyridinoline cross-links (nmol/mmol crt)	2612 ± 2064	1436 ± 518	1571 ± 662	211-395	NS
Deoxypyridinoline cross-links (nmol/mmol crt)	757 ± 893.7	369.3 ± 305.9	465.3 ± 522.9	33-5-75.9	NS

NS, Not significant.

Measures of bone formation and breakdown were monitored just before disodium pamidronate infusion at 0, 1, 3, 6, 12, 18, and 24 months. Osteoblastic activity was measured by plasma alkaline phosphatase with a kit method from Sigma Diagnostics and osteocalcin by IRMA (Nichols Institute Diagnostics) with intra-assay and interassay coefficients of variation of 7% and 9%, respectively. These were compared with values from a normal age-matched control group. Osteoclastic activity was measured by total pyridinoline and deoxypyridinoline cross-links by an in-house method with 24-hour urinary acid hydrolysis, chromatography extraction, and high-performance liquid chromatography analysis, with correction for urinary creatinine. Intra-assay and interassay coefficients of variation were 8% and 10% for pyridinoline cross-links and deoxypyridinoline cross-links, respectively. Biochemical data were compared with those of a normal age-matched control population. Urine was collected for all specimens, 2 hours after the patients rose in the morning.

Bone mineral density was assessed at 0, 12, and 24 months with dual-energy x-ray absorptiometry (DEXA Hologic 1000) with precision of 1% at the lumbar spine and 2% at the hip.

Biopsy of affected bone was undertaken during any intercurrent orthopedic procedure that was necessary during the 2 years of treatment. Sections were decalcified before the examination was performed.

Echocardiography was performed at 0, 12, and 24 months with calculation of cardiac output by measurement of time velocity integrals of Doppler trace across the aortic valve, where

$$\text{Stroke volume} = \text{Time velocity integral} \times \text{Cross-sectional area (cm}^2\text{)}.$$

RESULTS

Clinical

Patients reported marked reduction in bone pain within the first week of their first treatment, with a sustained increase in mobility after pain ceased. Most patients had complete cessation of pain that lasted a minimum of 5 months but pain tended to return just before the next infusion was due. Objective evidence of change was difficult to assess because of variability in mobility and age-related changes in locomotion during the trial. Two children stopped using a wheelchair completely for the duration of the study. Fracture incidence was reduced in 5 patients by a mean of 3.4 to 2.4 fractures per year, but 1 child sustained more fractures in the first year of treatment (from 3 to 5), because he ceased using his wheelchair and joined the school cricket team. A 4-year-old child had an increased number of fractures, again because of increased mobility (including climbing on tables). All parents reported a consistent improvement in sleep pattern (sleeping through the night compared with waking with reports of bone pain) and qual-

ity of life for their affected offspring. Objective quality-of-life scales were not used, because such major changes were not anticipated. Resting pulse rate and skin temperature decreased in the 4 children who had initial clinical evidence of a high cardiac output state. Resolution of the visual field defect occurred in patient 6 after 6 months of treatment and did not recur throughout the 2 years.

No new endocrinopathy occurred during the 2 years of treatment. There was no clinical or biochemical progression of the liver disorder in patient 2 during the 2 years of the study. The 2 patients (1 and 2) who had clinical evidence of precocious puberty had no pubertal progress during the next 2 years. Patients 3 and 4 had increased testicular size to 6 mL bilaterally after completion of the study at ages 11 and 6 years, respectively. T_3 thyrotoxicosis developed in patient 1 at 1 year after completion of the study.

When surgery was necessary for management of fractures and bone deformity, all procedures were performed by a single orthopedic surgeon, who reported improvement in the texture and cortical thickness of long bones with successful instrumentation, whereas there had been several previous failed attempts to achieve fixation of intramedullary rods because of softness of bone. Twelve separate rodding procedures were performed on 5 children with the use of Sheffield intramedullary expanding rods. All procedures were

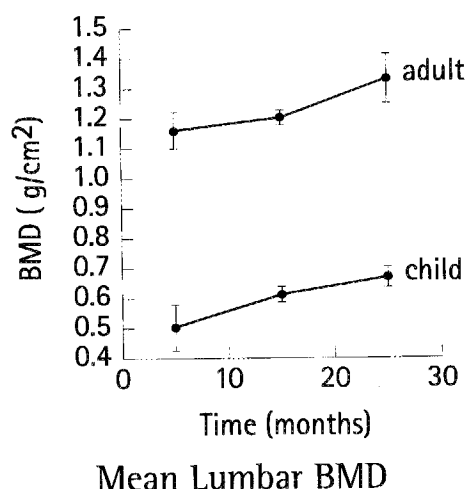


Fig 1. Mean areal bone density (BMD) at lumbar spine and whole body BMD during 2 years of bisphosphonate treatment.

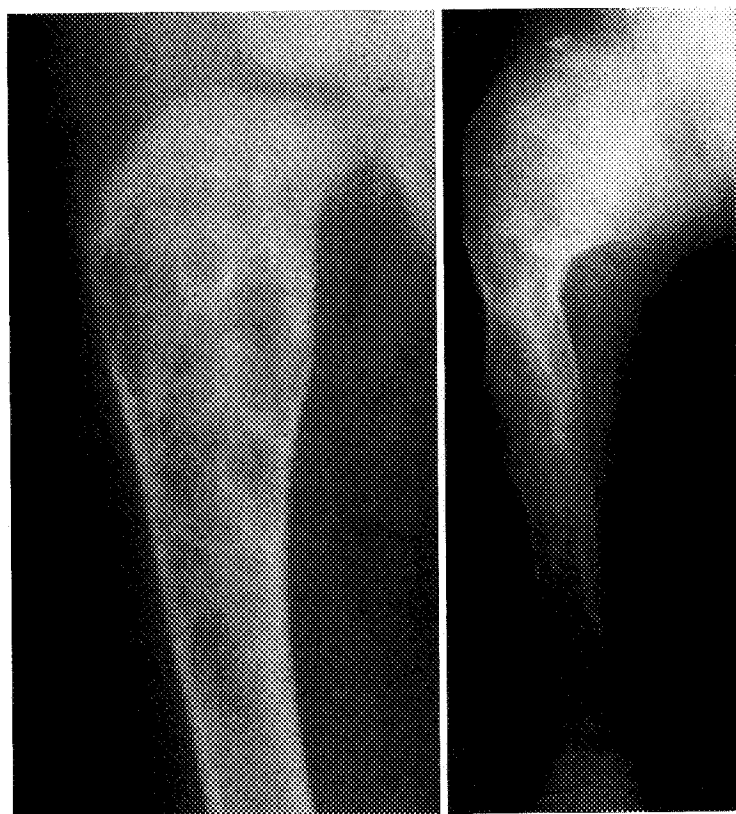


Fig 2. Fibrous dysplasia in subject 1 demonstrating bony expansion and distortion of the femur over 4-year period, making Δ BMD calculations impossible. *Left*, Age 3 years; *right*, age 7 years.

successful and resulted in independent mobility for all patients.

Side effects were limited to a mild acute phase reaction on first exposure to bisphosphonate with fever to 38.5°C

for 24 hours in older children and young adults. No child younger than age 5 years was febrile.

There were no other side effects at any time throughout the 2 years of the study.

Biochemical

Changes in bone turnover values were difficult to assess, correlating with intercurrent fracture or surgical interventions (Table II). There was a slight trend towards decrease in bone turnover in the first 12 months of treatment in the children that was not consistent or maintained. Several of the assay samples for the young adults were unavailable because of loss in transit. However, all available samples were in the normal adult range. Data calculation was made for children only with the use of unpaired *t* tests. Full blood count, renal function, and liver function were normal throughout the study in all patients except patient 2, in whom liver function was abnormal before bisphosphonate administration and did not change throughout the study. Follicle stimulating hormone, luteinizing hormone, and testosterone levels were in the prepubertal range in patients 1 and 2 throughout the 2 years of the study.

Bone Mineral Density

BMD values increased at both the lumbar spine and the whole body in all patients throughout the 2 years of study, with a significant mean 34.6% increase at the lumbar spine in children ($P < .002$) (Δz score +1.27) and 3.4% ($P < .005$) (Δz score +0.56) increase in adults (Fig 1, Table III). Only 1 adult patient (7) had a single thoracic vertebra affected with fibrous dysplasia. Her lumbar vertebrae were radiologically normal, as were those of all other patients. Accurate calculation of volumetric BMD at the hip or calculation of BMD adjusted for body size and growth was impossible because of the grossly abnormal and changing bony configuration in this area in all pediatric patients (Fig 2).

Biopsy of bone affected with fibrous dysplasia was undertaken in 4 children during intercurrent surgical procedures, with biopsies of subjects 1, 3, 4, and 5 done before and during bisphosphonate treatment. Typical pathologic

Table III. Changes in areal BMD (g/cm²) during 2 years of pamidronate treatment

Area	Time (mo)	Children			Adults		
		Mean BMD	Mean z score	P value	Mean BMD	Mean z score	P value
Lumbar	0	0.5 ± 0.08	-0.73		1.16 ± 0.06	0.22	
	24	0.67 ± 0.03	+1.0	.002	1.33 ± 0.08	0.78	.005
Whole body (excluding lower limbs)	0	0.82 ± 0.06			0.97 ± 0.07		
	24	0.94 ± 0.07		NS	1.06 ± 0.06		NS

NS, Not significant.

changes of fibrous dysplasia were seen in all biopsies. Before treatment was performed, biopsies from subjects 1, 3, and 4 also demonstrated giant cell reparative granuloma-like areas. Before treatment was performed, biopsies from patients 1 and 3 demonstrated areas of cartilage and of lamellar bone mixed with woven bone. These changes continued to occur (on repeated biopsies) during treatment.

Echocardiography

In the 5 children examined, a variable and inconsistent reduction in cardiac output was recorded, with mean cardiac output before treatment of 4.96 ± 0.75 L/min, falling to 3.84 ± 0.38 L/min at 12 months and rising to 4.73 ± 0.29 L/min by 24 months (not significant).

DISCUSSION

This study confirms the sustained clinical improvement in bone pain, mobility, and quality of life seen in other clinical studies of patients with the McCune Albright syndrome and other bone conditions such as adult Paget's disease and pediatric osteogenesis imperfecta.^{10,12,16,18,19} The reasons for cessation of bone pain are complex and may reflect a combination of decreased bone turnover, specific alterations in cytokine release, and reduction in microfractures, with decreased osteoclast action resulting in decreased bone re-

sorption and increased bone strength, with filling in of lytic lesions.¹⁴ Objective measurement of clinical improvement is very difficult to demonstrate in these children because of necessary intercurrent orthopedic procedures, intercurrent fractures, and variability in pediatric markers of bone turnover.²⁰ Our group as a whole had a decreased fracture rate during 2 years of treatment, presumably because of improved bone density and quality and improved cortical thickness.

Despite only small alterations in biochemical or bone density measures in our subjects, the surgical interventions were more successful (7 failed surgical procedures before treatment compared with 12 successful roddings after treatment), reflecting a more major change in overall bone strength with treatment than could be shown with conventional measurements. Reduced osteoclast action and decreased bone resorption with a net increase in cortical and trabecular volume and width induced by bisphosphonate treatment are the likely reasons for improved surgical outcome.

A case report of alendronate effect on BMD suggests that major improvements in bone quality with filling of lytic lesions and improved cortical thickness occur with this treatment also.²¹

Alteration in BMD in children must be assessed in the context of normal growth and increasing body size. Increased lumbar spine BMD seen in the children in this study is consistent with

expected areal increases after 2 years of growth, with a calculated prepubertal increase in areal BMD of 2% to 5% per year being normal. Because bisphosphonate is taken up preferentially into bone affected with fibrous dysplasia, it is not expected that areal BMD of unaffected areas would alter significantly other than by a growth effect. Although our patients had increasing BMD as they grew, the changes were due to a mixture of normal linear growth, filling in of lytic lesions, and perhaps alterations in bony architecture. BMD of affected areas is not a useful modality to monitor the effect of treatment because of the extreme distortion of bony architecture in the peripheral skeleton, with increased cross-sectional area of bone making interpretation unreliable, because the large area gives a falsely elevated areal BMD. Volumetric bone density remains static during childhood in normal bone but increases in fibrous dysplasia as the affected areas expand.

Whole body BMD calculations were made on the basis of truncal bone density to include head, pelvis, and upper limbs and thus include the variable areas of fibrous dysplasia. Lower limbs were excluded from analysis because of the insertion of metal rods. The z scores could not be calculated for the unusual combination of areas measured. Expression of the results as a mean percentage increase in BMD to include areas of fibrous dysplasia was

considered the only way in which to look for an objective measurement of bone density.

There are various ways in which bisphosphonate may be exerting an effect on the bone lesions of the McCune Albright syndrome in addition to its direct effect as an osteoclast inhibitor with reduced bone resorption and a net increase in bone quality. Interleukin 6 synthesis in PFD has been postulated (as a downstream effector of cyclic adenosine monophosphate activity) to have a possible pathogenic role in the bone lesions by increasing the number of osteoclasts.²² This effect may be modulated effectively by the use of disodium pamidronate as an inhibitor of osteoclast activity. C fos proto-oncogene expression is increased in bone biopsy specimens from patients with PFD²³ and in human osteogenic sarcomata (seen in 0.6% to 6% of patients with McCune Albright syndrome).²⁴ Increased expression of c fos by PFD lesions suggests that it may be the first step in the multistep carcinogenesis process. Bisphosphonate treatment by binding to bone surfaces and altering bone turnover in a multitude of ways may be effective not only in improving overall BMD but also in possibly decreasing future carcinogenic risk by decreasing c fos transcription.

The regimen of treatment described here has caused considerable clinical improvement in mobility, pain, and quality of life in affected children and adults. However, all patients noticed return of bone pain before the next infusion (6 months apart). More frequent cycles of treatment may decrease this problem. Pamidronate is rapidly absorbed from the circulation and bound to bone surfaces. More frequent treatment cycles at a lower dose could be more effective in terms of both reduced osteoclast activity and bone turnover, with improved symptom control. The single case report of a young adult treated with Alendronate suggests it may be a useful option for treatment, but its potential side effects may be a

concern when children are treated, and dosing schedules remain to be established for the growing skeleton.

Decreased bone turnover may decrease cardiac output as a result of reduced blood flow through bone, leading in turn to reduced long-term cardiac morbidity and risk of late cardiomyopathy. Normalization of bone remodeling during treatment with reduction in bony deformity as seen in the resolution of a visual field defect in one of our patients suggests that bisphosphonate treatment may be beneficial for this problem with reduced need for aggressive surgical intervention.²⁵

Chondroid areas with apparent demineralization have been reported in biopsy specimens of patients treated for PFD with disodium pamidronate.¹⁰ However, the fibrous dysplasia is progressive during childhood, and massive chondroid differentiation in untreated PFD has previously been reported.²⁶ Those reported post-treatment biopsy specimens may have reflected a problem present before treatment. Other studies of bisphosphonate use in children have not reported mineralization defects in bone biopsy specimens obtained during treatment.²⁷ These lesions were present in 2 of our subjects before treatment and did not change during treatment, again suggesting that chondroid differentiation may occur independent of bisphosphonate.

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